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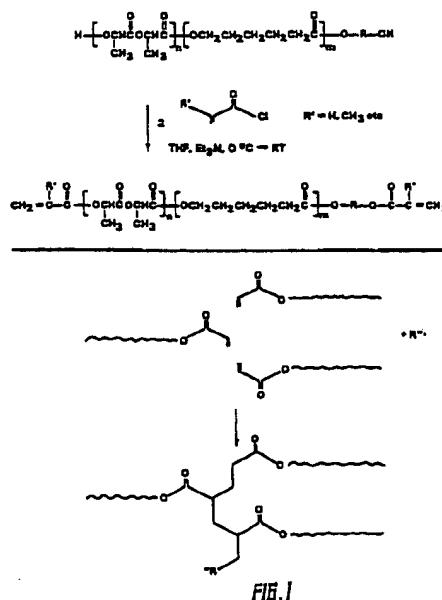
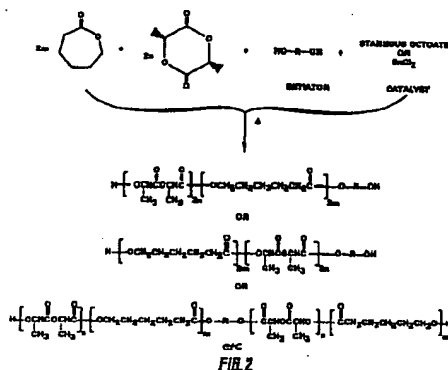
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(54) Biodegradable in-situ forming implants

(57) A biodegradable thermosetting polymer system is provided for use in providing syringeable, in-situ forming, solid biodegradable implants for animals. The polymer is placed into the animal in liquid form and cures to form the implant in-situ. The thermosetting system comprises mixing together effective amounts of a liquid acrylic ester terminated, biodegradable prepolymer and a curing agent, placing the liquid mixture within an animal and allowing the prepolymer to cure to form the implant. The system provides a syringeable, solid biodegradable delivery system by the addition of an effective level of biologically active agent to the liquid before injection into the body.



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Description

Technical Field

5 The present invention relates to a system of biodegradable polymers, and more particularly to the use of such polymer system for providing syringeable, in-situ forming, solid, biodegradable implants.

Background Art

10 Thermoset biodegradable polymers have been previously described for use in medical applications. These polymers have been formed by crosslinking reactions which lead to high-molecular-weight materials that do not melt or form flowable liquids at high temperatures. Typical examples of these materials are the crosslinked polyurethanes described in U.S. Patent No. 2,933,477 to Hostettler and U.S. Patent No. 3,186,971 to Hostettler et al. Copolymers based on ϵ -caprolactone and L-lactide or DL-lactide crosslinked via peroxide initiators were described in U.S. Patent Nos. 4,045,418 and 4,057,537, both to Sinclair. Crosslinked caprolactone copolymers have been prepared by incorporation of a bislactone into a monomer feed, as described in U.S. Patent No. 4,379,138 to Pitt et al. Trihydroxy-functional copolymers of ϵ -caprolactone and ϵ -valerolactone have been crosslinked with diisocyanates, thereby affording biodegradable polymers, as described in Pitt et al., J. Polym. Sci.: Part A: Polym Chem. 25:955-966; 1987. These polymers are also solids when crosslinked or cured.

20 Although this class of biodegradable polymers have many useful biomedical applications, there are several important limitations to their use in the body where body is defined as that of humans, animals, birds, fish, and reptiles. Because these polymers are solids, all instances involving their use have required initially forming the polymeric structures outside the body, followed by insertion of the solid structure into the body. For example, sutures, clips, and staples are all formed from thermoplastic biodegradable polymers prior to use. When inserted into the body, they retain their original shape rather than flow to fill voids or cavities where they may be most needed.

25 Similarly, drug-delivery systems using these biodegradable polymers have to be formed outside the body. In such instances, the drug is incorporated into the polymer and the mixture shaped into a certain form such a cylinder, disc, or fiber for implantation. With such solid implants, the drug-delivery system has to be inserted into the body through an incision. These incisions are often larger than desired by the medical profession and lead to a reluctance of the patients to accept such an implant or drug-delivery system.

30 The only way to avoid the incision with these polymers is to inject them as small particles, microspheres, or microcapsules. These may or may not contain a drug which can be released into the body. Although these small particles can be injected into the body with a syringe, they do not always satisfy the demand for a biodegradable implant. Because they are particles, they do not form a continuous film or solid implant with the structural integrity needed for certain prostheses. When inserted into certain body cavities such as the mouth, a periodontal pocket, the eye, or the vagina where there is considerable fluid flow, these small particles, microspheres, or microcapsules are poorly retained because of their small size and discontinuous nature. In addition, microspheres or microcapsules prepared from these polymers and containing drugs for release into the body are sometimes difficult to produce on a large scale, and their storage and injection characteristics present problems. Furthermore, one other major limitation of the microcapsule or small-particle system is their lack of reversibility without extensive surgical intervention. That is, if there are complications after they have been injected, it is considerably more difficult to remove them from the body than with solid implants.

Therefore, there exists a need for a system which provides a biodegradable, polymeric structure useful in overcoming the above-described limitations.

35 There exists a further need for a system for providing syringeable, in-situ forming, solid, biodegradable implants which can be used as prosthetic devices and/or controlled delivery systems.

Moreover, there exists a need for such a system which can provide implants having a range of properties from soft to rigid, so as to be usable with both soft and hard tissue.

Disclosure of the Invention

50 The present invention relates to a biodegradable thermosetting polymer system comprising a liquid biodegradable thermosetting prepolymer for forming an implant in situ within a body by placing the system into the body and curing it. The thermosetting system does not contain solvents and is usually cured by means of a curing agent.

It further relates to the use of a biodegradable thermosetting polymer for the preparation of a biodegradable thermosetting system for forming an implant in situ within a body by placing the system into the body and curing it. The thermosetting polymer is usually cured by means of a curing agent.

Therefore, the present invention relates to systems of biodegradable polymers forming in situ prosthetic implants and controlled-release, drug-delivery systems which can be administered as liquids via, for example, a syringe and needle, but which cure ("set") shortly after dosing to form a solid. The implants are biodegradable because they are made

from biodegradable thermosetting polymers.

The placement of the system can be anywhere within the body, including soft tissue such as muscle or fat, hard tissue such as bone, or a cavity such as the periodontal, oral, vaginal, rectal, nasal, or a pocket such as a periodontal pocket or the cul-de-sac of the eye. For drug-delivery systems, the biologically active agent is added to the polymer system where it is either dissolved to form a homogeneous solution or dispersed to form a suspension or dispersion of drug within the polymeric system. In the body the system forms an implant thereby trapping or encapsulating the drug within the polymeric matrix as the implant solidifies. The release of the drug then follows the general rules for diffusion or dissolution of a drug from within a polymeric matrix.

The thermosetting system comprises the synthesis of crosslinkable polymers which are biodegradable and which can be formed and cured in-situ. The thermosetting system comprises reactive, liquid, oligomeric polymers which contain no solvents and which cure in place to form solids, usually with the addition of a curing catalyst.

The multifunctional polymers useful in the thermosetting system are first synthesized via copolymerization of either DL-lactide or L-lactide with ϵ -caprolactone using a multifunctional polyol initiator and a catalyst to form polyol-terminated prepolymers. The polyol-terminated prepolymers are then converted to acrylic ester-terminated prepolymers, preferably by acylation of the alcohol terminus with acryloyl chloride via a Schotten-Baumann-like technique, i.e., reaction of acyl halides with alcohols. The acrylic ester-terminated prepolymers may also be synthesized in a number of other ways, including but not limited to, reaction of carboxylic acids (i.e., acrylic or methacrylic acid) with alcohols, reaction of carboxylic acid esters (i.e., methyl acrylate or methyl methacrylate) with alcohols by transesterification, and reaction of isocyanatoalkyl acrylates (i.e., isocyanatoethyl methacrylate) with alcohols.

The liquid acrylic-terminated prepolymer is cured, preferably by the addition of benzoyl peroxide or azobisisobutyronitrile, to a more solid structure. Thus, for an implant utilizing these crosslinkable polymers, the catalyst is added to the liquid acrylic-terminated prepolymer immediately prior to injection into the body. Once inside the body, the crosslinking reaction will proceed until sufficient molecular weight has been obtained to cause the polymer to solidify. The liquid prepolymer, when injected, will flow into the cavity or space in which it is placed and assume that shape when it solidifies. For drug delivery utilizing this system, biologically active agents are added to the liquid polymer systems in the uncatalyzed state.

With the thermosetting systems, the advantages of liquid application are achieved. For example, the polymer may be injected via syringe and needle into a body while it is in liquid form and then left in-situ to form a solid biodegradable implant structure. The need to form an incision is eliminated, and the implant will assume the shape of its cavity. Furthermore, a drug-delivery vehicle may be provided by adding a biologically active agent to the liquid prior to injection. Once the implant is formed, it will release the agent to the body and then biodegrade. The term "biologically active agent" means a drug or some other substance capable of producing an effect on a body.

It is an object of the present invention, therefore, to provide a thermosetting system for producing biodegradable polymeric implants.

It is also an object of the present invention to provide such a polymer system which may be useful in producing syringeable, in-situ forming, solid biodegradable implants.

It is a further object of the present invention to provide such an implant which can be used in a controlled-release delivery system for biological agents.

It is a further object of the present invention to provide implants having a range of properties from soft and elastomeric to hard and rigid, so as to be usable with both soft and hard tissue.

Brief Description of the Figures and Tables

Fig. 1 illustrates the synthesis of acrylate-terminated prepolymers and subsequent crosslinking by free-radical initiators;

Fig. 2 illustrates structures for the random copolymer of ϵ -caprolactone and L-lactide initiated with a diol;

Table 1 is a summary of the bifunctional PLC prepolymers synthesized;

Table 2 is a summary of the acrylic ester terminated prepolymers synthesized; and

Table 3 is a summary of curing studies.

Best Mode of Carrying Out the Invention

The present invention relates to biodegradable, thermosetting systems for forming implants in situ. The present invention also relates to a liquid biodegradable polymeric system that can be injected into a body where it forms a solid and releases a biologically active agent at a controlled rate. The biodegradable polymeric systems comprise thermo-

setting polymers that are liquids without the use of solvents.

In one envisioned use of the thermosetting system, the polymer system is placed in a syringe and injected through a needle into the body. Once in place, the polymer solidifies, and a solid structure is formed. The implant will adhere to its surrounding tissue or bone by mechanical forces and can assume the shape of its surrounding cavity. Thus, the biodegradable polymer system can be injected subdermally like collagen to build up tissue or to fill in defects. It can also be injected into wounds including burn wounds to prevent the formation of deep scars. Unlike collagen, the degradation time of the implant can be varied from a few weeks to years depending upon the polymer selected and its molecular weight. The injectable polymer system can also be used to mend bone defects or to provide a continuous matrix when other solid biodegradable implants such as hydroxyapatite plugs are inserted into bone gaps. The injectable system can also be used to adhere tissue to tissue or other implants to tissue by virtue of its mechanical bonding or encapsulation of tissue and prosthetic devices.

Another envisioned use of the thermosetting system is to provide a drug-delivery system. In this use, a bioactive agent is added to the polymer system prior to injection, and then the polymer agent mixture is injected into the body. In some cases, the drug will also be soluble in the system, and a homogeneous liquid system of polymer and drug will be available for injection.

In other cases, the drug will not be soluble in the system, and a suspension or dispersion of the drug in the polymer system will result. This suspension or dispersion can also be injected into the body.

In either case, the polymer will solidify and entrap or encase the drug within the solid matrix. The release of drug from these solid implants will follow the same general rules for release of a drug from a monolithic polymeric device. The release of drug can be affected by the size and shape of the implant, the loading of drug within the implant, the permeability factors involving the drug and the particular polymer, and the degradation of the polymer. Depending upon the bioactive agent selected for delivery, the above parameters can be adjusted by one skilled in the art of drug delivery to give the desired rate and duration of release.

The term drug or bioactive (biologically active) agent as used herein includes without limitation physiologically or pharmacologically active substances that act locally or systemically in the body. Representative drugs and biologically active agents to be used with the syringeable, in-situ forming solid implant systems include, without limitation, peptide drugs, protein drugs, desensitizing agents, antigens, vaccines, anti-infectives, antibiotics, antimicrobials, antiallergenics, steroidal anti-inflammatory agents, decongestants, miotics, anticholinergics, sympathomimetics, sedatives, hypnotics, psychic energizers, tranquilizers, androgenic steroids, estrogens, progestational agents, humoral agents, prostaglandins, analgesics, antispasmodics, antimalarials, antihistamines, cardioactive agents, non-steroidal anti-inflammatory agents, antiparkinsonian agents, antihypertensive agents, β -adrenergic blocking agents, nutritional agents, and the benzophenanthridine alkaloids. To those skilled in the art, other drugs or biologically active agents that can be released in an aqueous environment can be utilized in the described injectable delivery system. Also, various forms of the drugs or biologically active agents may be used. These include without limitation forms such as uncharged molecules, molecular complexes, salts, ethers, esters, amides, etc., which are biologically activated when injected into the body.

The amount of drug or biologically active agent incorporated into the injectable, in-situ, solid forming implant depends upon the desired release profile, the concentration of drug required for a biological effect, and the length of time that the drug has to be released for treatment. There is no critical upper limit on the amount of drug incorporated into the polymer system except for that of an acceptable solution or dispersion viscosity for injection through a syringe needle. The lower limit of drug incorporated into the delivery system is dependent simply upon the activity of the drug and the length of time needed for treatment.

In all cases, the solid implant formed within the injectable polymer system will slowly biodegrade within the body and allow natural tissue to grow and replace the implant as it disappears. Thus, when the material is injected into a soft-tissue defect, it will fill that defect and provide a scaffold for natural collagen tissue to grow. This collagen tissue will gradually replace the biodegradable polymer. With hard tissue such as bone, the biodegradable polymer will support the growth of new bone cells which will also gradually replace the degrading polymer. For drug-delivery systems, the solid implant formed from the injectable system will release the drug contained within its matrix at a controlled rate until the drug is depleted. With certain drugs, the polymer will degrade after the drug has been completely released. With other drugs such as peptides or proteins, the drug will be completely released only after the polymer has degraded to a point where the non-diffusing drug has been exposed to the body fluids.

The injectable, in-situ forming biodegradable implants can also be produced by crosslinking appropriately functionalized biodegradable polymers. The thermosetting system comprises reactive, liquid, oligomeric polymers which cure in place to form solids, usually with the addition of a curing catalyst. Although any of the biodegradable polymers previously described for the thermoplastic system can be used, the limiting criteria is that low-molecular-weight oligomers of these polymers or copolymers must be liquids and they must have functional groups on the ends of the prepolymer which can be reacted with acryloyl chloride to produce acrylic ester capped prepolymers.

The preferred biodegradable system is that produced from poly(DL-lactide-co-caprolactone), or "DL-PLC". Low-molecular-weight polymers or oligomers produced from these materials are flowable liquids at room temperature.

Hydroxy-terminated PLC prepolymers may be synthesized via copolymerization of DL-lactide or L-lactide and ϵ -caprolactone with a multifunctional polyol initiator and a catalyst. Catalysts useful for the preparation of these prepolymers are preferably basic or neutral ester-interchange (transesterification) catalysts. Metallic esters of carboxylic acids containing up to 18 carbon atoms such as formic, acetic, lauric, stearic, and benzoic are normally used as such catalysts. Stannous octoate and stannous chloride are the preferred catalysts, both for reasons of FDA compliance and performance.

If a bifunctional polyester is desired, a bifunctional chain initiator such as ethylene glycol is employed. A trifunctional initiator such as trimethylolpropane produces a trifunctional polymer, etc. The amount of chain initiator used determines the resultant molecular weight of the polymer or copolymer. At high concentrations of chain initiator, the assumption is made that one bifunctional initiator molecule initiates only one polymer chain. On the other hand, when the concentration of bifunctional initiator is very low, each initiator molecule can initiate two polymer chains. In any case, the polymer chains are terminated by hydroxyl groups, as seen in Figure 1. In this example, the assumption has been made that only one polymer chain is initiated per bifunctional initiator molecule. This assumption allows the calculation of a theoretical molecular weight for the prepolymers.

A list of the bifunctional PLC prepolymers that were synthesized is given in Table 1. Appropriate amounts of DL-lactide, ϵ -caprolactone, and ethylene glycol were combined in a flask under nitrogen and then heated in an oil bath at 155° C to melt and mix the monomers. The copolymerizations were then catalyzed by the addition of 0.03 to 0.05 wt % SnCl_2 . The reaction was allowed to proceed overnight. The hydroxyl numbers of the prepolymers were determined by standard titration procedure. The Gardner-Holdt viscosities of the liquid prepolymers were also determined using the procedures outlined in ASTM D 1545. The highest molecular-weight prepolymer (MW = 5000) was a solid at room temperature; therefore, its Gardner-Holdt viscosity could not be determined.

The diol prepolymers were converted to acrylic-ester-capped prepolymers via a reaction with acryloyl chloride under Schotten-Baumann-like conditions, as seen in Figure 2 and summarized in Table 2. Other methods of converting the diol prepolymers to acrylic-ester-capped prepolymers may also be employed.

Both THF and dichloromethane were evaluated as solvents in the acylation reactions. Several problems were encountered when THF was used as the solvent. The triethylamine hydrochloride formed as a by-product in the reaction was so finely divided that it could not be efficiently removed from the reaction mixture by filtration. Triethylamine hydrochloride ($\text{Et}_3\text{N} \cdot \text{HCl}$) has been reported to cause polymerization of acrylic species (U.S. Patent No. 4,405,798). In several instances, where attempts to remove all of the $\text{Et}_3\text{N} \cdot \text{HCl}$ failed, the acrylic-ester-capped prepolymers gelled prematurely. Thus, to effectively remove all of the $\text{Et}_3\text{N} \cdot \text{HCl}$, it was necessary to extract the prepolymers with water. For reactions carried out in THF, it is preferred that one first evaporate the THF in vacuo, redissolve the oil in CH_2Cl_2 , filter out the $\text{Et}_3\text{N} \cdot \text{HCl}$, and then extract the CH_2Cl_2 layer with water. Stable emulsions were sometimes encountered during extraction. The acylations were later carried out in CH_2Cl_2 instead of THF. The filtration of $\text{Et}_3\text{N} \cdot \text{HCl}$ from the reaction mixture was found to be much easier using this solvent, and the organic fraction could be extracted directly with water after filtration.

Both diol and acrylic prepolymers were examined by IR and ^1H NMR spectroscopy. The salient feature of the IR spectra of diol prepolymers is a prominent O-H stretch centered at approximately 3510 cm^{-1} . Upon acylation, the intensity of the O-H stretch decreases markedly, and new absorbances at approximately 1640 cm^{-1} appear. These new absorbances are attributed to the C=C stretch associated with acrylic groups. Likewise, the presences of acrylic ester groups is apparent in the ^1H NMR spectra, the characteristic resonances for the vinyl protons falling in the range of 5.9 to 6.6 ppm.

The acrylic prepolymers and diol prepolymers were then cured, as summarized in Table 3. The general procedure for the curing of the prepolymers is now described: to 5.0 g of acrylic prepolymer contained in a small beaker was added a solution of benzoyl peroxide (BP) in approximately 1 mL of CH_2Cl_2 . In some cases, fillers or additional acrylic monomers were added to the prepolymers prior to the introduction of the BP solution. The mixtures were stirred thoroughly and then poured into small petri dishes. The dishes were placed in a preheated vacuum oven for curing. Some of the samples were cured in air and not in vacuo, and these samples are so indicated in Table 3.

This thermosetting system may be used wherever a biodegradable implant is desired. For example, because the prepolymer remains a liquid for a short time after addition of the curing agent, the liquid prepolymer/curing agent mixture may be placed into a syringe and injected into a body. The mixture then solidifies in-situ, thereby providing an implant without an incision. Furthermore, a drug-delivery system may be provided by adding a biologically active agent to the prepolymer prior to injection. Once in-situ, the system will cure to a solid; eventually, it will biodegrade, and the agent will be gradually released.

DETAILED DESCRIPTION OF EXAMPLE

The following example is set forth as representative of the present invention. The example is not to be construed as limiting the scope of the invention as this and other equivalent embodiments will be apparent in view of the present disclosure, figures, and accompanying claims.

EXAMPLE 1

An illustrative method for the synthesis of an acrylate terminated prepolymer is described. To an oven-dried, 500-mL, three-necked, round-bottom flask fitted with an addition funnel, gas inlet adapter, mechanical stirrer assembly, and rubber septum was added, under nitrogen, 100.0 g of difunctional hydroxy-terminated prepolymer and 200 mL of freshly distilled THF (from CaH_2). The flask was cooled in an ice bath, and 24 mL of dry triethylamine (0.95 equiv/equiv OH) was added via a syringe. The addition funnel was charged with 15.4 g of acryloyl chloride (0.95 equiv/equiv OH) in 15 mL of THF, and the solution was added dropwise to the stirred reaction mixture over 1 hour. The mixture was stirred overnight and allowed to reach room temperature. The precipitated triethylamine hydrochloride was removed by filtration, and the filtrate was evaporated in vacuo, affording a pale yellow oil, which was the acrylate-terminated prepolymer. The acylations employing CH_2Cl_2 as solvent were conducted in a similar manner. However, the reaction times at 0°C were shortened to 1 hour, whereupon the reaction mixtures were allowed to reach room temperature over 1 hour. $\text{Et}_3\text{N} \cdot \text{HCl}$ was filtered out, additional CH_2Cl_2 (approximately 800 mL) was added to the filtrate, and the filtrate was extracted several times with 250 mL portions of water. The organic layer was dried over $\text{MgSO}_4/\text{Na}_2\text{SO}_4$, filtered, and reduced to an oil in vacuo. The bottles of acrylic prepolymers were wrapped in foil and stored in a refrigerator to safeguard against premature crosslinking.

TABLE 1. SUMMARY OF DIOL PREPOLYMERS SYNTHESIZED

Sample no.	Mole ratio of monomers to initiator (ethylene glycol - 1.0)		Catalyst (SnCl ₄), Theoretical wt % M _n , daltons	Hydroxyl No., meq OH (56.1)/g		Gardner Holdt viscosity, approx. Stokes (T - 22.2 °C)
	DL-lactide	ε-caprolactone		Observed	Theoretical	
C964-114-1	2.4	5.0	0.03	993	100	113
C964-124-1	6.1	32.8	0.05	5036	19.7	22.3
C964-128-1	2.5	5.0	0.03	993	103	113
C964-136-1	8.0	8.0	0.03	2128	48 (est.)	52.7
						28.0
						Solid
						28.2
						1375

TABLE 2. SUMMARY OF ACRYLIC ESTER TERMINATED PREPOLYMERS SYNTHESIZED

Sample no.	Diol precursor sample no.	Estimated concentration of acrylic groups, meq/g	Reaction conditions			Comments
			Temp, °C	Time, h	Solvent	
C964-118-1	C964-114-1	1.78	0-RT	17	THF	No problems, stable.
C964-125-1	C964-114-1	1.78	0-RT	17	THF	Gelled. Overnight exposure to Et ₃ N·HCl at RT..
C964-132-1	C964-128-1	1.84	0	2	THF	100 ppm MENQ added before workup.
C964-137-1	C964-128-1	1.84	0	2	Et ₂ O	Difficult workup. Low yield.
C964-139-1	C964-136-1	0.81	0	2	THF	Gelled. Overnight exposure to residual Et ₃ N·HCl in refrigerator.
C964-144-1	C964-136-1	0.81	0	1	CH ₂ Cl ₂	No problems, stable.
C964-146-1	C964-124-1	0.33	0	1	CH ₂ Cl ₂	No problems, stable.

TABLE 3. SUMMARY OF CURING STUDIES

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives, wt %	Curing Temp. °C	conditions Time, h	Initial Shore A hardness	Comments
C964-120-1	C964-118-1	2.0	none	82	16	ND ^a	Rubbery, breaks when bent 180°, weak.
C964-120-2	C964-118-1	1.0	none	82	16	83	Less brittle than C964-120-1.
C964-121-1	C964-118-1	2.0	none	82	16	77	Rubbery, breaks when bent 180°, weak.
C964-121-2	C964-118-1	1.0	none	82	16	80	Slightly stronger than C964-121-1.
C964-121-3	C964-118-1	0.5	none	82	16	78	Slightly more elastic than C964-121-2
C964-121-4	C964-118-1	0.1	none	82	16	69	Same as C964-121-3.

(continued)

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-122-1	C964-118-1	1.0	TMPIETA ^b 46	82	2.5	94	Less rubbery than C964-120 and C964-121; brittle.
C964-122-2	C964-118-1	0.5	TMPIETA 46	82	2.5	91	Same as C964-122-1, more flexible
C964-122-3	C964-118-1	1.0	TMPIETA 175	82	2.5	95	Not rubbery at all, brittle, weak.
C964-122-4	C964-118-1	0.5	TMPIETA 175	82	2.5	93	Similar to C964-122-3.

(continued)

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-123-1	C964-118-1	0.1	TMPTETA 46	82	2.5	89	Rubbery, stronger than C964-120 and C964-121, not flexible.
C964-123-2	C964-118-1	0.25	TMPTETA 46	82	2.5	83	About the same as C964-123-1, may be more brittle.
C964-123-3	C964-118-1	0.1	TMPTETA 175	82	2.5	92	Not rubbery; strong, brittle.
C964-134-1	C964-132-1	0.05 (AIBN) ^c	none	60 ^d	17	Liquid	No cure.
C964-134-2	C964-132-1	0.10 (AIBN)	none	60 ^d	17	Liquid	No cure.

(continued)

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-134-3	C964-132-1	0.24 (AIBN)	none	60 ^d	17	Liquid	No cure.
C964-134-4	C964-132-1	0.50 (AIBN)	none	60 ^d	17	Liquid	No cure.
C964-134-5	C964-132-1	1.00 (AIBN)	none	60 ^d	17	Liquid	Slightly thickened.
C964-135-1	C964-132-1	0.05	none	80 ^d	17	Liquid	No cure.
C964-135-2	C964-132-1	0.10	none	80 ^d	17	Liquid	No cure.
C964-135-3	C964-132-1	0.25	none	80 ^d	17	Liquid	No cure.
C964-135-4	C964-132-1	0.50	none	80 ^d	17	Liquid	No cure.
C964-135-5	C964-132-1	1.00	none	80 ^d	17	Liquid	Slightly thickened
C964-135-6	C964-128-1 ^e	0.05	none	80 ^d	17	Liquid	No cure.
C964-135-7	C964-128-1 ^e	0.10	none	80 ^d	17	Liquid	No cure.
C964-135-8	C964-128-1 ^e	0.25	none	80 ^d	17	Liquid	No cure.

(continued)

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-135-9	C964-128-1 ^a	0.50	none	80 ^d	17	Liquid	No cure.
C964-135-10	C964-128-1 ^a	1.00	none	80 ^d	17	Liquid	No cure.
C964-135-11	C964-124-1 ^a	0.05	none	80 ^d	17	ND	No cure.
C964-135-12	C964-124-1 ^a	0.10	none	80 ^d	17	ND	No cure.
C964-135-13	C964-124-1 ^a	0.25	none	80 ^d	17	ND	No cure.
C964-135-14	C964-124-1 ^a	0.50	none	80 ^d	17	ND	No cure.
C964-135-15	C964-124-1 ^a	1.00	none	80 ^d	17	ND	No cure.
C964-141-1	C964-137-1	0.10	none	80	1	66	Flexible elastomer.
C964-141-2	C964-137-1	0.25	none	80	1	71	Flexible elastomer.
C964-141-3	C964-137-1	0.50	none	80	1	72	Flexible elastomer.

(continued)

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-141-4	C964-137-1	1.00	none	80	1	72	Flexible elastomer.
C964-141-5	C964-128-1	0.10	none	80	1	Liquid	No cure.
C964-141-6	C964-128-1	0.25	none	80	1	Liquid	No cure.
C964-141-7	C964-128-1	0.50	none	80	1	Liquid	No cure.
C964-141-8	C964-128-1	1.00	none	80	1	Liquid	No cure.
C964-143-1	C964-137-1	0.25	Cab-o-Sil PTG, 5.0	80	1	74	No cure.
C964-143-2	C964-137-1	0.25	Cab-o-Sil PTG, 2.0	80	1	73	No cure.
C964-143-3	C964-137-1	0.25	L-PLA (IV=0.8), 5.0	80	1	75	No cure.
C964-143-4	C964-137-1	0.25	L-PLA (IV=0.8), 2.5	80	1	78	No cure.

(continued)

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-148-1	C964-144-1	0.5	none	80	17	Liquid	No cure.
C964-148-2	C964-144-1	0.10	none	80	17	Liquid	No cure.
C964-148-3	C964-144-1	0.25	none	80	2	66	C964-148-4 and C964-148-6 were about the same in toughness, and both were better than C964-148-3 and C964-148-5.

(continued)

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-148-4	C964-144-1	0.50	none	80	2	68	C964-148-4 and C964-148-6 were about the same in toughness, and both were better than C964-148-3 and C964-148-5.

(continued)

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-148-5	C964-144-1	1.00	none	80	2	67	C964-148-4 and C964-148-6 were about the same in toughness, and both were better than C964-148-3 and C964-148-5.

(continued)

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-148-6	C964-144-1	2.00	none	80	2	69	C964-148-4 and C964-148-6 were about the same in toughness, and both were better than C964-148-3 and C964-148-5.
C964-149-1	C964-144-1	0.15	none	80	2	64	
C964-149-2	C964-144-1	0.20	none	80	2	64	
C964-149-3	C964-144-1	0.25	none	80	2	66	

(continued).

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-149-4	C964-144-1	0.15	Cab-O-Sil N70-JS 5.0	80	2	ND	Samples too porous, did not have any flat area for hardness measurement.
C964-149-5	C964-144-1	0.20	Cab-O-Sil N70-JS 5.0	80	2	ND	Samples too porous, did not have any flat area for hardness measurement.
C964-149-6	C964-144-1	0.25	Cab-O-Sil N70-JS 5.0	80	2	ND	Samples too porous, did not have any flat area for hardness measurement.
C964-150-1	C964-146-1	0.05	none	80	17	ND	Only partially cured.

(continued)

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-150-2	C964-146-1	0.10	none	80	2	72	Elastic, flexible, moderately strong.
C964-150-3	C964-146-1	0.25	none	80	2	57	Elastic, flexible, moderately strong.
C964-150-4	C964-146-1	0.50	none	80	2	56	Elastic, flexible, moderately strong.
C964-150-5	C964-146-1	1.00	none	80	2	50	Elastic, flexible, moderately strong.

(continued)

TABLE 3. SUMMARY OF CURING STUDIES (continued)

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives wt %	<u>Curing conditions</u>		Initial Shore A hardness	Comments
				Temp. °C	Time, h		
C964-150-6	C964-146-1	2.00	none	80	2	51	Elastic, flexible, moderately strong.

^aResult not determined.
^bTMPTETA = trimethylolpropane triethoxy triacrylate.
^cAIEN = azobisisobutyronitrile.
^dCured in air at atmospheric pressure.
^eDiol prepolymer used.

Claims

1. A biodegradable thermosetting polymer system comprising a liquid biodegradabl thermosetting prepolymer for

forming an implant in situ within a body by placing the system into the body and curing it.

2. A system of claims 1, wherein the prepolymer is an acrylic-ester-terminated prepolymer.

3. A system of claim 2, wherein the prepolymer is synthesized via copolymerization of DL-lactide with ϵ -caprolactone.

4. A system of claim 2, wherein the prepolymer is synthesized via copolymerization of L-lactide with ϵ -caprolactone.

5. A system of claim 3 or 4, wherein the prepolymer is formed by said copolymerization with a polyol initiator.

6. A system of any one of claims 3-5, wherein a catalyst is added to the copolymerization step.

7. A system of claim 6, wherein the catalyst is stannous octoate or stannous chloride.

8. A system of any one of claims 1-7, containing also a curing agent

9. A system of claim 8 for forming a solid implant in situ within a body by mixing the prepolymer and the curing agent and placing the system into the body and curing it.

10. A system of claim 9, wherein the curing agent is azobisisobutyronitrile or benzoyl peroxide.

11. A system of claim 9 or 10, containing a biologically active agent which is released by diffusion or erosion as the implant biodegrades.

12. A system of any one of claims 1-11, wherein the system is syringeable.

13. A system of any one of claims 1-12 for forming an implant in a periodontal pocket or in dental extraction sites.

14. A system of any one of claims 1-12 for forming an implant in a bone defect or in a wound.

15. A system of any one of claims 1-12 for forming an implant for adhering tissue to tissue or another implant to tissue.

16. A system of any one of claims 1-12 for forming an implant for building up tissue or for filling in a defect.

17. The use of a biodegradable thermosetting prepolymer for the preparation of a biodegradable thermosetting polymer system according to claims 1-12 for forming an implant in situ within a body by placing the system into the body and curing it.

18. The use of claim 17, wherein the implant is for a periodontal pocket or for dental extraction sites.

19. The use of claim 17, wherein the implant is for a bone defect or for a wound.

20. The use of claim 17, wherein the implant is for adhering tissue to tissue or for another implant to tissue.

21. The use of claim 17, wherein the implant is for building up tissue or for filling in a defect.

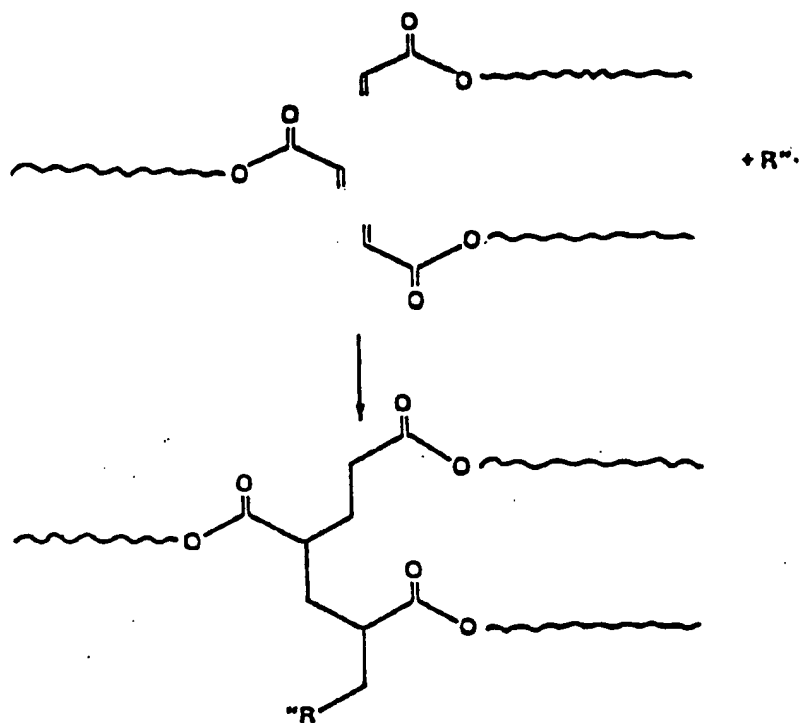
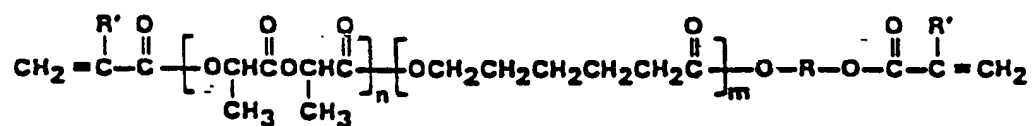
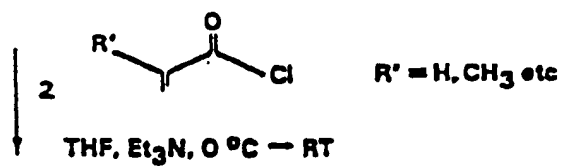
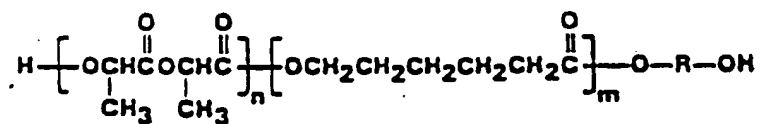


FIG. 1

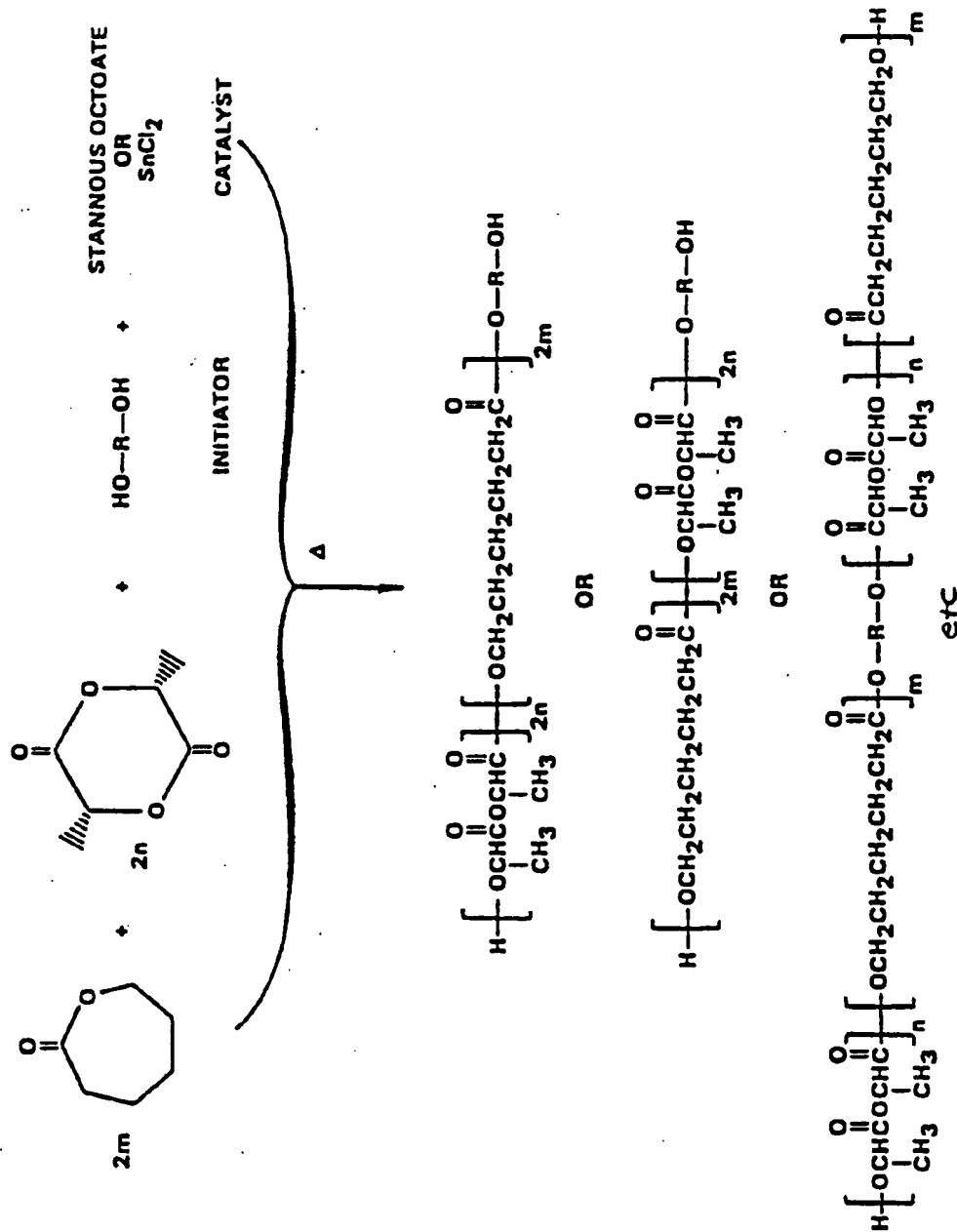


FIG. 2



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 96 11 4933

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP 0 271 831 A (DENTSPLY INT INC) 22 June 1988 * claims; examples 1-15 *	1	A61L27/00 A61K9/20 A61K9/00
A	WO 85 00969 A (SKY POLYMERS) 14 March 1985 * claims; examples 1-4 *	1-21	
A	EP 0 140 766 A (FORSYTH DENTAL INFIRMARY) 8 May 1985		
A	US 3 219 527 A (BENJAMIN F. GURNEY) 23 November 1965		
A	US 3 887 699 A (YOLLES SEYMOUR) 3 June 1975		
A	US 4 677 139 A (FEINMANN BERNHARD P P ET AL) 30 June 1987		
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			A61L A61K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 7 March 1997	Examiner ESPINOSA, M
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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